REMARKS

Claims 1-21 are pending in the present application. Claim 1 has been amended to recite "with" instead of "by", in response to the Examiner's objection concerning an informality. Applicants have also amended claim 15, to more accurately describe the methods of the present invention. The amendment is supported at least in the specification at page 10, 2nd ¶, and does not contain new matter. Applicants respectfully request reconsideration of the Examiner's rejections, in light of the following remarks.

Double Patenting

The Examiner rejected claim 1 under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claim 3 of U.S. patent no. 6.331,235 ('235). The Examiner also rejected claim 2 as allegedly being obviousness-type double patenting over claims 2 and 3 of the '235 patent. Furthermore, the Examiner rejected claim 3 as allegedly being obviousness-type double patenting over claim 3 of the '235 patent. Finally, the Examiner rejected claims 4-21 as allegedly being obviousness-type double patenting over claims 4-21 of the '235 patent. Applicants respectfully request that these rejections be held in abeyance until allowance of the pending claims.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-21 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner indicated that "stereoisomers.," in claim 1, line 10, should be –stereoisomers.-- The specification as filed does not recite the term "stereoisomers.,". Thus, it appears that this rejection was made in error, and Applicants respectfully respect that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

I. Claims 1, 3-13 and 20 are Nonobvious under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.*

The Examiner rejected claims 1, 3-13 and 20 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Dixon *et al.* (J. Chromatog. 802: 386-380 [1998]) in view of Jamieson *et al.*, (Leukemia Res. 14: 209-219 [1990]); Wu *et al.*, (J. Liq. Chromatog. 1795: 1111-24 [1994]), Fanali *et al.*, (J. Capillary Electrophor. 1: 72-8 [1994]); Armstrong *et al.* (Anal. Chem. 65: 1114-17 [1993]; and Yao *et al.* (J. Chromatog. 637: 195-200 [1993]). Applicants must respectfully disagree for the reasons below.

As the Examiner concedes, Dixon does not mention benzoporphyrin derivatives, a clinical sample, or a chiral selector. (Office Action, page 8). However, the Examiner alleges that "Dixon et al. does teach separating stereoisomers of porphyrin derivatives that have six-membered aromatic ring substituents, which are analogous to benzoporphyrins and can indeed be construed as benzoporphyrin 'derivatives.'" (Office Action, page 9). The Examiner also alleged that "the benzoporphyrin stereoisomers separated the [sic] Dixon et al. are analogous to benzophorphyrin [sic] derivatives, if not in fact benzoporphyrin derivatives." *Id.* Applicants must respectfully disagree.

First, there is no motivation to combine the references. In particular, none of the references cited by the Examiner relate to methods for separating stereoisomers of benzoporphyrin derivatives. Dixon *et al.* describe the separation of atropisomers of 5,10,15,20-tetrakis(N-methyl-2-pyridiniumyl)-21H,23H-porphyrin (TMPyP(2)), whose structure is reproduced in Exhibit 1 for the Examiner's convenience. Contrary to the Examiner's assertions, the pyridinium porphyrins described in Dixon *et al.* are not benzoporphyrin derivatives. For the Examiner's convenience, various benzoporphyrin derivatives (BPD) described in Figure 1 of the specification are reproduced in Exhibit 2.

As shown in Figure 1, benzoporphyrin derivatives have an asymmetric porphyrin core structure. In particular, benzoporphyrin derivatives have a phenylene ring fused to one side of the porphyrin core structure. In contrast, the pyridinium porphyrins described in Dixon *et al.* have a symmetric porphyrin core structure, with four identical pyridinyls substituent at each meso position.

Furthermore, the properties of benzoporphyrin derivatives shown in Figure 1 are different from the pyridinium porphyrins described in Dixon. For example, BPDs contain ionizable carboxylic acid groups, which are absent in the pyridinium porphyrins described in Dixon. Unlike the pyridinium porphyrins, BPD enantiomers are very easily hydrolyzed at high pH (See e.g., Specification at page 9, 2nd ¶). The side chain propionic acid of BPD enantiomers also begins to deprotonate when the pH of the buffer is above about 3.5. (Specification at 10).

Although Jamieson *et al.* relates to benzoporphyrin derivatives, this reference describes the preferential uptake of BPD by leukemic versus normal cells. To rely on a reference under 35 U.S.C. § 103, it must be analogous prior art. "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the invention is concerned." MPEP 2141.01 (a) (quoting *In re Oetiker*, 977 F.2d 1443, 1446). Jamieson *et al.* only describe the capacity of BPD to accumulate selectively in leukemic cells. (Jamieson *et al.*, page 217). Because Jamieson *et al.* do not relate to screening methods at all, it is considered non-analogous art, and the combination is improper.

Fanali *et al.* and Armstrong *et al.* describe the use of cyclodextrins in capillary electrophoresis. Fanali *et al.* describe use of cyclodextrins to separate optical isomers, including amino acid enantiomers and pharmaceutical compounds such as ergot alkaloids, sympathomimetic drugs, beta-blockers, and anticoagulants. (Fanali *et al.*, pages 75-76). Armstrong *et al.* describe the use of capillary columns containing immobilized cyclodextrin coatings for separation methods. (Armstrong *et al.*, page 1117). However, both references are silent regarding the separation of porphyrins, let alone benzoporphyrin derivatives.

Wu *et al.* (J. Liq. Chromatog. 17: 1111-1124 (1994)) describe the separation of five porphyrin carboxylic acids (*i.e.*, uroporphyrin, heptacarboxylporphyrin, hexacarboxyporphyrin, pentacarboxylporphyrin, and coproporphyrin). This reference does not teach methods of separating benzoporphyrins, let alone benzoporphyrin stereoisomers. For the Examiner's convenience, the porphyrins separated in Wu *et al.* are reproduced in Exhibit 3.

Yu *et al.* describe the capillary electrophoretic separation of nine porphyrins having two to eight acid side-chains using a systematic optimization scheme based on the overlapping resolution mapping method. (See, Abstract). The compounds separated are described in Figure 1, which included mesoporphyrin IX, deuteroporphyrin IX, protoporphyrin IX, pentacarboxylporphyrin I, hexaarboxylporphyrin I, heptacarboxyporphyrin I, uroporphyrin I, zinc protoporphyrin IX and coproporphyrin I. Contrary to the methods of the present invention, Yao *et al.* do not teach methods of separating benzoporphyrins, let alone benzoporphyrin stereoisomers. Unlike benzoporphyrins which have an asymmetric porphyrin core structure, the porphyrins studied in Yao *et al.* all have symmetric core structures. For the Examiner's convenience, the porphyrins separated in Yao *et al.* are reproduced in Exhibit 4.

Second, even if combined, the combination does not teach the presently claimed invention. As previously indicated, none of the references, alone or in combination with Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.*, relate to separating benzoporphyrin stereoisomers using capillary electrophoresis.

Third, there is no reasonable expectation of success that the methods taught in Dixon *et al.*, alone or in combination with Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.* would be successful in separating benzoporphyrin stereoisomers. As previously indicated, benzoporphyrin derivatives have an asymmetric porphyrin core structure, and are different from the other porphyrins studied which all have a symmetric porphyrin core. Thus, there is no reasonable expectation of success that methods used to separate porphyrins having a symmetric porphyrin core would be successful in separating benzoporphyrins.

Based on the above, claim 1 is unobvious under Dixon, in combination with Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.* Because claim 1 is nonobvious under the cited references, dependent claims 3-13 and 20 are also nonobvious under the cited references. Applicants therefore respectfully request that this rejection be withdrawn.

II. Claims 2, 17-19 and 21 are Nonobvious under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.*, Further in view of Wu *et al.*

The Examiner also rejected claims 2, 17-19 and 21 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.*, further in view of Wu *et al.* (J. Liq. Chromatog. 17: 1917-1979 [1994]). In particular, the Examiner alleges that "[i]t would have been obvious . . . at the time the invention was made to use a laser-induced fluorescence (LIF) detection system in the invention as taught by Wu et al. in the invention of Dixon et al. as modified by Jamieson et al., Wu et al. (CAPLUS), Fanali et al., and Armstrong et al." (Office Action, page 12-13). Applicants must again respectfully disagree.

The failure of this combination to teach the presently claimed invention is not remedied by further combining the cited references with Wu *et al.* (J. Liq. Chromatog.). Wu *et al.* describe the separation of coproporphyrin isomers, and are silent regarding benzoporphyrin separation. For the Examiner's convenience, the porphyrin structures studied in Wu *et al.* are reproduced in Exhibit 5. As previously indicated, coproporphyrins have a symmetric porphyrin core, unlike benzoporphyrins. Thus, claims 2, 17-19 and 21 are nonobvious under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.* (CAPLUS), Yao *et al.*, further in view of Wu *et al.* (J. Liq. Chromatog.). Applicants therefore respectfully request that this rejection be withdrawn.

III. Claims 14-16 are Nonobvious under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.*, Further in view of Chan *et al.*

The Examiner also rejected claims 14-16 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.*, further in view of Chan *et al.* In particular, the Examiner indicates that Chan "presents results that allow comparisons of separations with phosphate to separations with borate.... Barring evidence to the contrary, . . . it would have been obvious to one with ordinary skill in the art . . . to use borate as a buffer, because as shown by Chan it offers acceptable separations" (Office Action, page 15). Applicants must again respectfully disagree.

The failure of the combination of Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.*, and Yao *et al.* to teach the presently claimed invention is not remedied by further combining Chan *et al.* (J. Chromatog. 636: 171-178 [1993]). Chan *et al.* describe the use of capillary electrophoresis and micellar electrokinetic capillary chromatography to separate components in polyhaematoporphyrin (PHP). As indicated in the abstract, PHP is known to contain haematoporphyrin (HP), protoporphyrin (PP), hydroxyethylvinyldeuteroporphyin (HVD), and a mixture of ester, ether and carbon-carbon linked oligomers. Contrary to the present invention, Chan *et al.* do not teach separation of benzoporphyrin stereoisomers. Thus, claims 2, 17-19 and 21 are nonobvious under Dixon *et al.*, Jamieson *et al.*, Fanali *et al.*, Armstrong *et al.*, Wu *et al.* (CAPLUS), Yao *et al.*, further in view of Chan *et al.* Applicants therefore respectfully request that this rejection be withdrawn.

Information Disclosure Statement

The Examiner has also requested a copy of the Stalcup *et al.* article (Stalcup et al. Anal. Chem. 66: 3054-3059 [1994]), which was previously cited in the IDS submitted on May 31, 2002. This reference, along with Fanali et al. (J. Capillary Electrophor. 1: 72-8 [1994]) and Wu et al. (J. Liq. Chromatogr. 1795:1111-24 [1994]), are submitted in a Supplemental IDS. CAPLUS abstracts of Fanali et al. and Wu et al. were cited in the present Office Action. Copies of these articles are submitted for the Examiner's convenience.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection

with the filing of this document to Deposit Account No. 03-1952 referencing docket no.273012010901. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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